

NATIONAL INSTITUTES OF HEALTH

Office of the Director

SIGNIFICANT ITEMS IN SENATE APPROPRIATIONS COMMITTEE REPORT

The following section represents FY 2003 Congressional requirements for reports and significant items derived from Senate Report 107-216. These actions discussed below are contingent on inclusion of similar language and funding in the final FY 2003 appropriation and related reports. Additional items may be transmitted at a later date as a result of the final Conference report.

Item

Alpha-1 antitrypsin deficiency - Alpha-1- antitrypsin deficiency, a genetic disorder often misdiagnosed as asthma or chronic obstructive pulmonary disease (COPPED), is a major cause of lung transplants in adults and liver transplants in children. The Committee encourages the NIH to enhance its clinical research portfolio for alpha-1 and to consider conducting a state-of-the-science conference on the disorder. The National Institutes of Health (NIH) is also encouraged to raise public awareness about alpha-1 and provide appropriate information to health professionals. (p. 148)

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) currently funds a variety of clinical and basic research studies of alpha-1 antitrypsin (AT) deficiency as a contributor to emphysema due to insufficiency of an enzyme that prevents the breakdown of lung tissue. They include investigations of the molecular mechanisms that impair secretion of AT; methods of gene therapy delivery; and approaches to increase the availability of defective, but partially active, AT. NHLBI-supported investigators are defining the abnormalities and degradation pathways of the AT protein, characterizing the inflammation that leads to disease in various AT deficiency states, and evaluating the possibility of treating the disease with drugs that would enhance the release of partially active protein from liver cells. A genetics study of families is seeking to identify other genes that may modify the nature and severity of the disease as expressed in different individuals. Finally, the NHLBI has co-sponsored a number of conferences on the state of the science in AT deficiency research, including an international scientific meeting organized by the Alpha-1 Foundation in September 2002, "Models of Emphysema: Speeding the Pace of Progress."

Item

Autoimmune diseases – The Committee awaits the imminent release of the NIH's Autoimmune Diseases Research Plan, which was requested in the Children's Health Act of 2000. More than 80 autoimmune diseases affect up to 22 million Americans,

mostly women. The Committee believes that planned research has the potential to generate improved prevention measures, diagnostic tools, and treatment regimens, resulting in reduced treatment costs and a significant alleviation of human suffering. (p. 148)

Action taken

The National Institutes of Health (NIH) remains deeply committed to research to improve the diagnosis, prevention, and treatment of autoimmune diseases. In December 2002, NIH transmitted the NIH Autoimmune Diseases Research Plan to Congress, in fulfillment of the requirements for a plan and biennial report under the Children's Health Act of 2000 (PL. 106-310).

The Plan highlights many unprecedented opportunities to increase the understanding of autoimmune diseases, with a conceptual focus on the underlying mechanisms shared by many autoimmune diseases. Understanding the commonalities of this family of heterogeneous diseases may facilitate the translation of new knowledge into more effective treatment and prevention strategies. The Plan describes four areas central to progress for all autoimmune diseases and offers recommendations for addressing them. These areas are: burden of disease; etiology; treatment, prevention, and diagnosis; and training, education, and information dissemination.

The NIH Autoimmune Diseases Research Plan was prepared by the NIH Autoimmune Diseases Coordinating Committee (ADCC) and reviewed by an expert panel that included scientists, clinicians, and representatives from constituency groups. The ADCC., which was established in 1998, under the direction of the National Institutes of Allergy and Infectious Diseases, facilitates collaboration among those NIH Institutes, Offices, and Centers, other Federal agencies, and private organizations with an interest in autoimmune diseases. In FY 2003, the NIH ADCC. will continue its efforts to coordinate and enhance autoimmune diseases research among the various Federal and private entities that conduct autoimmunity research, education, and outreach, and implement the recommendations of the NIH Autoimmune Diseases Research Plan.

Item

Chronic fatigue syndrome – The Committee is pleased that the NIH released its long-awaited CFS program announcement in December 2001, and it hopes that this initiative will reverse 7 years of declining CFS funding at NIH. To foster response to this program announcement, the Committee urges the NIH to put a priority on efforts to understand the cause and progression of CFS, identify diagnostic markers, and better understand pediatric CFS. (p. 148/149)

Action taken or to be taken

For more than a decade the Office of Research on Women's Health (ORWH) has worked in concert with the NIH Institutes and Centers (ICs), other Federal agencies, and the

research, healthcare, policy and advocacy communities to foster and support a comprehensive approach to research on women's health. The ORWH is particularly interested in, and has as an integral part of its mission, the study of multisystemic diseases, such as CFS, from which proportionately more women than men suffer.

The study of CFS, and all multisystemic illnesses, requires a thorough multidisciplinary approach that encompasses the scientific mission of many NIH ICs; therefore, the ORWH has assumed responsibility for coordinating CFS research efforts through a Trans-NIH Working Group on Chronic Fatigue Syndrome Research (CFSWG) and spearheaded the above mentioned program announcement (<http://grants.nih.gov/grants/guide/pa-files/PA-02-034.html>) to stimulate and broaden the scope of CFS research. This announcement, based on recommendations from the October 2000 State of the Science Symposium, is sponsored by eleven NIH ICs and encourages basic, clinical and translational research on the causes, consequences and treatment of CFS in diverse groups across the lifespan. The CFSWG plans to assess the effectiveness of this PA after three funding cycles have passed and is prepared to issue specific requests for applications (RFAs) if independent investigators have not addressed the full range of research possibilities.

The ORWH expanded its website to include more CFS related scientific materials for researchers and continues to work with other government (e.g. CDC) and nongovernmental agencies (e.g. CFIDS of America) to foster CFS research programs. A CFSWG subcommittee has begun to develop coordinated programs for encouraging CFS research and navigating the NIH funding process for presentation at diverse scientific conferences. We anticipate that these efforts will encourage research applications. The ORWH, through the CFSWG, plans to hold a scientific workshop on the interface between the brain and immune systems: *Basic Mechanisms in Chronic Fatigue Syndrome: Neuro-Immune Mechanisms* in June 2003 to stimulate research interest among the intramural scientific community as well as to provide the scientific basis on which to initiate an interdisciplinary RFA. Studies in response to such an RFA will be expected to address CFS research in the context of both sex and gender differences as well as ethnic disparities. We expect this initiative to contribute significantly to an important understanding of CFS and other multisystemic illnesses, many overlapping, studied at the NIH.

After these steps have been fully implemented over the next several years, an interdisciplinary panel of scientific experts will be convened to evaluate the scientific products of these efforts and prioritize recommendations for a future research agenda.

Item

Distribution of resources - Following the Institute of Medicine (IOM) study of the organization of the NIH, the Committee encourages NIH to contract with IOM to study the distribution of research resources across the agency's Institutes and Centers. An objective analysis may help inform the committee on the wisest distribution of new funds as they become available. (p. 149)

Action taken or to be taken

The NIH priority setting process is outlined in NIH's booklet entitled, "Setting Research Priorities at the National Institutes of Health"

<http://public-council.nih.gov/SettingResearchPriorities.htm>.

There are several guiding principles that NIH uses to establish priorities. In addition to our commitment to support scientific work of the highest caliber, we also take into consideration the following: responsibility to capitalize on the potential for scientific progress; consideration of the measures that constitute the burden of disease to the nation and the individual; a need to maintain a diverse portfolio on a wide range of diseases; an obligation to ensure adequate support of the research infrastructure; and a need to seek advice from many sources, including the public. Each of NIH's Institutes and Centers has a broad and significant investment in efforts that seek to understand the many factors that encompass public health need. Assessing the many scientific opportunities and determining where to invest is a complex process that requires scientific

expertise across many disciplines and fields of inquiry. NIH is therefore in the best position to direct resource allocation, and we remain vigilant in our efforts to balance scientific opportunity with the health needs of our nation and the world.

In 1998, the Institute of Medicine (IOM) conducted a study on priority setting at the NIH and determined that overall NIH's priority setting process has served both NIH and the Nation well. The IOM made several recommendations to strengthen the process and NIH has successfully addressed those recommendations over the past several years.

Given the Committee's continued interest in resource allocation at the agency, the NIH will examine the need for an IOM study on the subject once the IOM study on the organization of NIH has been completed. The IOM expects to complete its report on that study by June 20, 2003.

Item

***Fibromyalgia* - Fibromyalgia is a chronic disorder characterized by widespread musculoskeletal pain, fatigue, multiple tender points, and other debilitating symptoms.** Because the symptoms manifest themselves most notably in the muscles, NIH research in fibromyalgia has been concentrated in the NIAMS. While the Committee commends the NIAMS for its interest in this condition, research increasingly indicates that fibromyalgia is not primarily a disease of the muscles, but rather a condition caused by malfunctions in the brain and central nervous system. Therefore, the Committee strongly urges the NIAMS and the NINDS to work together in addressing the challenge of fibromyalgia, and to expand their research into this disorder. In addition, the Committee notes that there are no FDA-approved drugs for fibromyalgia. While the NIAMS Strategic Plan for 2000-2004 specifically cites the need for NIAMS-supported investigators to test the efficacy of new drugs and biologicals for arthritis and related

diseases, the Institute has announced no plans to include fibromyalgia in that effort. The committee urges the NIAMS to do so. (p. 150)

Action taken or to be taken

The NIAMS has a growing interest and investment in research on fibromyalgia. Within the Institute's extramural program, the fibromyalgia portfolio is part of a newly created behavioral and prevention research program in the NIAMS' Rheumatic Diseases Branch.

This program has planned a series of initiatives that could benefit the fibromyalgia research community, including efforts to support multidisciplinary conferences on biobehavioral rheumatic diseases; training fellowships in behavioral rheumatology; and biopsychosocial approaches to studying rheumatic diseases. We expect these initiatives to complement our ongoing research and training efforts, which include support for a multidisciplinary, clinical research center focused on pediatric rheumatic diseases such as juvenile fibromyalgia. The Institute is also funding a new specialized center of research to study sex differences in pain sensitivity, in collaboration with the NIH Office of Research on Women's Health. A particular focus of this center will be to explore the neural basis of temporomandibular joint pain, a chronic condition that can affect fibromyalgia patients. The center will place a special emphasis on sex-related hypotheses for persistent, orofacial pain of deep tissue origin.

In the fall of 2002, in an effort to foster increased interactions in this area, the NIAMS conducted a program assessment meeting to review currently funded fibromyalgia projects across the NIH, discuss challenges in this area of study, and identify promising opportunities for future work. Scientific staff from a number of other NIH components took part in this workshop, in addition to invited extramural investigators and representatives of fibromyalgia patient organizations. In addition, the Institute has recently funded a clinical study to test the safety and efficacy of the medication gabapentin for the treatment of fibromyalgia symptoms. This project, the first to test this innovative therapy for fibromyalgia in a randomized, controlled trial, may fill an important treatment void for patients with this disorder. Furthermore, the Institute is developing an initiative to stimulate new research on fibromyalgia in children. At the National Institute of Neurological Disorders and Stroke, support continues for research on fibromyalgia, particularly with regard to the mechanisms in the brain and spinal cord that contribute to chronic muscle pain. The Institute also has a broad research program on the causes and treatment of chronic pain in general.

Item

Graduate Training in Clinical Investigation Awards –The Committee understands that the translation of basic research to general medical practice is slowed by a shortage of well-trained clinical investigators. The Committee is concerned that the NIH has not moved forward with implementation of the Graduate Training in Clinical Investigation Awards authorized by the Clinical Research Enhancement Act, which was intended to address this shortage. While the Committee is pleased that the NIH has initiated the Clinical Research Curriculum Awards to improve the quality of training in clinical research, a shortcoming of this program is the absence of support for tuition and stipends

for the individual students. The Committee believes that the Graduate Training in Clinical Investigation Awards may be necessary to replenish the supply of well-trained clinical investigators. (p. 150)

Action taken or to be taken

In direct response to the Clinical Research Enhancement Act, the NIH issued an announcement in FY 2001 (<http://grants2.nih.gov/grants/guide/rfa-files/RFA-RR-02-001.html>) of a new program, the Mentored Clinical Research Scholar Award (CRS, K12) to support graduate training and clinical investigation. This program is supported by the National Center for Research Resources (NCRR) to provide support to institutions to establish career development programs for physicians and dentists so they, in turn, may develop the research skills necessary to become independent, patient-oriented, clinical investigators. Funds provided by this award may be used for program candidate salary to support full or partial completion of an advanced degree such as an M.S. or Ph.D. in clinical investigation or an M.P.H. The maximum duration of support for a candidate is not to exceed five years. Candidates selected for the Clinical Research Scholar Award (CRS) program may be eligible for the NIH Loan Repayment Program for clinical investigators, which provides for repayment of the educational loan debt of physicians and dentists. The CRS award is an NCRR pilot program, which will be assessed in several years and possibly expanded.

Item

Human tissue supply – The Committee continues to be very interested in supporting the needs of researchers, particularly NIH grantees, as well as intramural and university-based researchers, who rely upon human tissues and organs to study human diseases and to search for cures. The Committee is aware that one of the leaders in this competitive field, the National Disease Research Interchange (NDRI), is positioned to serve such researchers who find it difficult to obtain these valuable and effective research resources. More than 500 peer-reviewed research advances have been published by the NDRI-supported researchers during the past 4 years, documenting the NDRI's contribution to our fund of knowledge. The Committee is greatly encouraged by these research advances and applauds the Director's expanded support for the NDRI by bringing the NEI, NIDDK, NIAID, NIAMS, and the Office of Rare Diseases into the multi-institute initiative. While this is promising, more needs to be done to match the expanding and unmet demand for the use of human tissue in research. The Committee, therefore, suggests that the Director advise the Director of the NCRR to consider an increase of its core support for NDRI, and to continue to encourage the Institute Directors NIH-wide to identify and implement program-specific initiatives that utilize NDRI resources. (p. 150/151)

Action taken or to be taken

The cooperative agreement through which the NDRI receives NIH support is effective through June 30, 2003. In accordance with NIH guidelines, this award will undergo competitive review in January 2003 to determine its suitability for continuation and recommended levels of support.

Item

Laboratory Animals - The Committee is concerned about allegations that several institutions receiving NIH funding may not be in full compliance with the Public Health Service policy on humane Care and Use of Laboratory Animals. The Committee encourages NIH to determine the extent and scope of any such allegations and notify the Committee of its findings. (p. 151)

Action taken or to be taken

The Office of Laboratory Animal Welfare (OLAW) provides oversight of more than 1,000 institutions which receive funding for research, teaching, and testing involving animals from the NIH and other agencies of the PHS. OLAW negotiates an Assurance of Animal Welfare—a document which commits the institution to comply with the PHS Policy on Humane Care and Use of Laboratory Animals—at least once every five years. It obligates institutions to conduct semiannual animal program reviews and facility inspections and provide annual reports as well as to report promptly any serious or continuing noncompliance with the PHS Policy, serious deviations from provisions of the Guide for the Care and Use of Laboratory Animals, and the suspension of any activity by the Institutional Animal Care and Use Committee to OLAW for evaluation. OLAW further exercises its oversight role by conducting a small number of site visits annually and exchanges information regarding compliance with the United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA) under a Memorandum of Understanding. It also receives reports from NIH funding components when their site visits turn up questionable practices, and occasionally receives, evaluates, and, if appropriate, investigates allegations from individuals and organizations. Unlike the USDA's oversight mechanism which is inspection-based, OLAW's is, as described above, Assurance-based. As a result and as expected, the vast majority of reports of noncompliance with the PHS Policy and serious deviations from provisions of the Guide come to us directly from the Assured institutions themselves. Considering that PHS funding supports the activities of thousands of investigators and their staffs in more than 1,000 institutions and involves hundreds of thousands of animals, it is not unexpected that some institutions are not in full compliance with the PHS Policy at any given time. In this regard, OLAW has been in contact with 125 institutions at which instances of noncompliance occurred this year. All of these cases have either been resolved or are on track for resolution in a timely manner.

Item

Minority health professions infrastructure – The Committee continues to be pleased with the NIH Director's implementation of various programs focused on developing research infrastructure at minority health professions institutions, including Research Centers at Minority Institutions, Extramural Biomedical Research Facilities, and the

National Center for Minority Health and Health Disparities. Because there are a number of new competitive mechanisms for the NIH to work with these research institutions, the Committee recommends that the NIH Director work closely with the Director of the National Center on Minority Health and Health Disparities to coordinate these various mechanisms. (p. 152)

Action taken or to be taken

The NIH Director and the NCMHD provided leadership for the development of a strategic research plan and budget to eradicate health disparities. The plan describes the cross-cutting nature of disease and scientific discovery and defines the scope of the problem of health disparities among the various minority and health disparity populations, specific objectives for addressing the problem, and the methods for advancing those objectives and for evaluating progress. Representing the collective commitment of all NIH Institutes and Centers (ICs), the plan focuses the attention of the NIH ICs on three major areas: 1) research, 2) research infrastructure, and 3) outreach. It includes individual submissions from all NIH ICs that highlight their areas of emphasis, objectives, action plans, timelines and performance measures for these three areas. The Strategic Research Plan, an evolving document, will be revised annually based on public comments received, public health need, scientific opportunity, and other factors. The Strategic Plan is undergoing final revision based on comments by the Department of Health and Human Services and will be forwarded to Congress in early 2003.

Advances in biomedical science depend on the availability of stable, well-maintained, state-of-the-art research environments. Such environments not only include novel research tools and technologies, but also facilitate collaboration among scientists and the sharing of expertise. The strategic plan highlights many IC programs focused on building infrastructure at minority health professions institutions. The NCMHD's Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT) was recently developed by the NCMHD to fund centers of excellence through partnerships that enable these institutions to maximize their health disparities research efforts. The NCMHD has collaborated with the National Center for Research Resources (NCRR) for several years to offer the Research Infrastructure in Minority Institutions (RIMI) Program. This program assists non-doctoral degree institutions in the development of their research infrastructure, primarily through collaborations with research-intensive universities. The NCRR also supports the Research Centers in Minority Institutions Program (RCMI). This program enhances the research capacity and infrastructure at minority colleges and universities that offer doctorate degrees in the health sciences.

The RIMI and the RCMI programs complement each other and allow the NCMHD and the NCRR to work closely in building the research infrastructure at minority health professions schools. The RIMI program helps to prepare non-doctoral degree institutions to advance to the RCMI level. Morgan State University, which received RIMI funds, recently assumed RCMI status.

This past year the NCMHD and NCRR recognized the need to increase support for

construction and major renovation of research facilities. The NCMHD and NCRR provided support to the Tuskegee University National Bioethics Center, consisting of a multi-layered bioethics and health care research infrastructure. Funding will be applied to bioethics-related research, training and community engagement among people of color. The effort was designed to frame an implementation strategy to guide the work of the Tuskegee University National Center for Bioethics in Health Care and Research. This funding proposal describes the proposed implementation and programmatic framework for a multi-layered intervention strategy for the Bioethics Center initiative. This strategy has the potential to fundamentally and systemically change the nation's health care infrastructure.

The NIH Director and the NCMHD Director will encourage the NIH ICs and the NCRR to increase their support for research infrastructure development at minority health professions institutions as viable opportunities become available.

Item

National Institutes of Health/Department of Energy Medical Technology Partnership –

The Committee expects the NIH to continue to collaborate with the Department of Energy (DOE) to evaluate the technologies developed within the nuclear weapons program and other DOE programs in terms of their potential to enhance health sciences, with the goal of achieving clinical applications and improved national health care. (p. 152)

Action taken or to be taken

The NIH recognizes the potential benefits associated with applying technologies developed within the DOE's programs at the nuclear weapons and multi-purpose laboratories to biomedical and clinical research. Efforts to support communication and identify applications of DOE technological resources to NIH programs are continuing and increasing. The DOE continues to be an active member of the NIH's Bioengineering Consortium (BECON) which coordinates multi-disciplinary research and training activities for all NIH institutes and other federal agencies. As part of DOE's participation in the BECON, national laboratory staff participated in key aspects of a major symposium on biosensors that was held at NIH in June 2002. Prior DOE/NIH communication and joint workshop initiatives have resulted in many NIH research grant applications and awards that include national laboratory staff. Some of these have been based on partnerships of DOE laboratories with other laboratories, academic institutions, and clinical entities and have facilitated transfer of DOE technologies to biomedical applications. The overall goals of the DOE/NIH collaborations are to achieve clinical applications, better health care, and improved quality of life consistent with national needs and agency missions.

Item

Neurofibromatosis (NF) – The Committee has included specific report language on NF under the NCI and NINDS, but it recognizes that NF research involves many other Institutes and Centers as well, including the NHLBI, NEI, NIDCD, NICHD, and NIAMS.

The Committee urges the Director to identify new research opportunities regarding NF that cuts across all these Institutes and Centers. (p. 152)

Action taken or to be taken

In addition to regular and ongoing dialogue about NF research needs and opportunities with other relevant institutes, the NINDS, NCI, NIDCD, NEI, NICHD, and NHLBI jointly sponsored the June 2002 meeting of the **National Neurofibromatosis Foundation International Consortium for the Molecular and Cell Biology of NF1 and NF2**, which identified new challenges and priorities in NF research. The NINDS and NCI continue to collaborate in implementing the recommendations put forth in the 2000 Brain Tumor Progress Review Group report, which includes recommendations specific to the neurofibromatoses.

Item

Office of Behavioral and Social Sciences Research (OBSSR) – The Committee encourages the OBSSR to foster the NIH's behavioral research portfolio by planning and sponsoring interdisciplinary initiatives that further the public health missions of multiple Institutes and Centers. In particular, the OBSSR's efforts to encourage research on new methodologies in the behavioral and social sciences are appreciated. The Office is urged to follow up on its conferences on sociocultural research and health disparities by developing initiatives with the National Center for Minority Health and Health Disparities and the NIH Institutes and Centers. The Committee encourages the OBSSR to push forward on planned initiatives to increase scientific understanding of the elements of education and the workplace that most affect health, and to follow up on its successful program of grants on behavior change by focusing on the challenge of maintaining behavior change. (p. 152/153)

Action taken or to be taken

The Office of Behavioral and Social Sciences Research (OBSSR) continues to foster the NIH's behavioral and social science research portfolio. **OBSSR is currently working with numerous interested ICs to develop workshops on interdisciplinary training in the behavioral, social and biomedical sciences. An OBSSR sponsored working group of scientists conducting community research identified ways by which OBSSR could facilitate community research initiatives to improve research methods and measure in the area. Based on recommendations from the workshop, collaborative activities among OBSSR and several NIH ICs are under development.**

As the Committee acknowledged above, OBSSR recognized the importance of providing support for the development of the tools for research. In FY 2002, OBSSR led a trans-NIH activity to develop and issue a program announcement in methodology and measurement in the behavioral and social sciences. This program announcement was issued in March 2002. Research was sought in areas such as the processes that underlie self reports, research design, data collection techniques, measurement, data analysis techniques, and related ethical issues. Future efforts will include strategies to develop and improve measurement of communities.

In FY 2002, OBSSR in collaboration with 15 NIH ICs, issued a program announcement calling for increased research on the influence of social and cultural factors on health and illness. The program announcement is the direct result of the OBSSR-sponsored conference on "Higher Levels of Analysis" and represents continuing efforts to achieve a better understanding of the interdependence of social, behavioral, and biological levels of analysis in health research. Topics addressed included sociocultural constructs such as race, ethnicity, socioeconomic status, and gender; sociocultural linkages between demographic factors and health; social and cultural factors in prevention, treatment, and health services; interpersonal, neighborhood, and community influences on health; health justice and ethical issues; and global perspectives on health.

Further, OBSSR and the National Center on Minority Health and Health Disparities sponsored research to expand the understanding of the economic implications of racial and ethnic health disparities in the United States, specifically to examine the potential economic benefit to society of research and resulting interventions that would eliminate disparities, to estimate the health care system costs associated with health disparities, to estimate the effects of health disparities on labor market performance, and to explore the evidence relating disparities in health to investments in education. The results of this research were presented at a symposium in FY 2002. Several of the research papers presented are currently under review and are expected to be published jointly. Additionally, in an effort to further understand the role of racial/ethnic bias in health disparities, OBSSR convened a meeting of leading scientists to present scientific evidence of the effects of racial and ethnic bias on health and to identify areas for future research to further explicate the relationship. A research agenda for understanding how racial bias may impact on health and how the effects might be ameliorated was developed. The recommendations from these activities will be used to provide guidance for trans-NIH program activities to fund research on racial bias and health.

Also, while the positive association between education and health has been well-documented, there is a paucity of scientific information on the biological mechanisms and the causal pathways which underpin this association. In October 2002, OBSSR cosponsored a workshop on Education Pathways to Health with the Princeton Center for Health and Well-being. The workshop recommended several areas for further research which will be pursued in a Request for Applications (RFA) to be jointly funded by OBSSR and several ICs in FY 2003 and 2004.

Mounting evidence suggests the need for research that examines biopsychosocial processes and tests interventions designed to achieve long-term health behavior change. Research efforts funded by a recent OBSSR-coordinated RFA were successful in achieving behavioral change during and immediately following the intervention phase. However, other research indicates that relapse rates for addictive behaviors, such as substance abuse and tobacco use, are very high. For example, most individuals who stop smoking cigarettes relapse within six months. Adherence to exercise, diet and other health regimens is no better, despite the fact that initial success rates for various behavior change programs are very good. Thus

long-term behavior change is as challenging, if not more so, than the initiation of behavior change. Past research efforts have typically focused on short term behavioral change. To follow-up on earlier efforts, in FY 2003, OBSSR will implement an initiative that will encourage investigators to expand on the current theoretical base of change processes and intervention models, to expand our understanding of how change, once achieved, is maintained over the long term.

Item

Office of Dietary Supplements (ODS)--The use of dietary supplements has increased significantly among Americans who want to improve their health and prevent disease, and there is a great need for additional research to better inform consumers of the benefits of these supplements. The Committee expects the ODS to allocate sufficient funds to continue an initiative--begun at the Committee's urging in last year's bill--to speed up ongoing collaborative efforts to develop, validate, and disseminate analytical methods and reference materials for the most commonly used botanicals and other dietary supplements.

The Committee is pleased that the ODS has followed through on its recommendation to begin a major research initiative on the safety and efficacy of products containing ephedra, and it urges the Office to assure that the work is reviewed in an unbiased manner before it is finalized. The results of this research should be evaluated by the FDA to assure that any regulatory action taken on products containing ephedrine alkaloids is based on sound science.

The Committee is also pleased that the ODS has begun an evidence-based review of the research concerning the health benefits of omega-3 fatty acids. Given the significant human and financial costs associated with heart disease, the Committee expects the Office to provide sufficient funds to promptly complete this initial review and provide recommendations for further major clinical trials. (p. 153)

Action taken and to be taken

The Office of Dietary Supplements (ODS) has embarked on an Analytical Methods and Reference Materials Program with Joseph Betz, Ph.D., as its Director. During the first few months of the program, ODS sponsored a Stakeholders meeting in order to identify the analytical needs of industry, regulatory agencies, health professionals, and consumers. The Stakeholders meeting was quickly followed by a workshop organized for the purpose of communicating the need for validation of methods and providing an overview of the process. In the first year of the program, Dr. Betz has established, along with colleagues in the FDA, a long-term funding arrangement with Association of Official Analytical Chemists (AOAC) International to validate existing methods for commonly used botanicals and other dietary supplements and a similar long-term arrangement with the National Institute of Standards and Technology (NIST) to develop standard reference

materials for some of the same materials. In the second year of the program, he plans to expand the AOAC International and NIST programs in order to accelerate the pace of methods validation while also soliciting the development of new analytical methods and reference materials using competitive grant and contract mechanisms.

ODS, in collaboration with the National Center for Complementary and Alternative Medicine (NCCAM), sponsored an evidence-based review of ephedra efficacy and safety through the Agency for Healthcare Research and Quality's (AHRQ) **Evidence-Based Practice Center program. The RAND-Southern California Center is completing the review, which contains systematic evaluation of all of the known clinical trials on ephedra for weight loss and athletic performance enhancement, as well as a large array of adverse events that may be associated with ephedra use. This review, scheduled for completion in early 2003, will form the basis for development of a research agenda. ODS and NCCAM will convene a working group of scientists to evaluate the research opportunities. In the meantime, ODS has worked with the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences to develop the appropriate animal models for evaluation of potential ephedra toxicity.**

ODS, in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) and other Institutes and Centers at NIH, worked to develop a task order for the systematic review of the health benefits of omega-3 fatty acids. AHRQ recently awarded this task order to a triad of Evidence-Based Practice Centers (RAND, University of Ottawa, and New England Medical Center) to provide a series of evidence reports on the health effects of omega-3 fatty acids on a number of body systems/conditions, primarily cardiovascular disease, but also including others such as infant growth and development, immune function, cancer, and mental disorders.

Item

[Online human embryonic stem cell registry] The Committee also commends NIH for the development of the online human embryonic stem cell registry and encourages NIH to expand the registry to make it more useful to researchers by providing additional documentation regarding the stem cell lines, such as conditions of derivation, characteristics of the cell lines (i.e. cell-surface markers present or absent, growth conditions, and requirements for maintenance in long-term culture), and publications that reference the cell lines. Furthermore, the Committee encourages NIH to seriously consider developing a stem cell repository. (p. 156)

Action taken or to be taken

At a recent meeting of the Task Force, the group agreed that the online NIH Human Embryonic Stem Cell Registry needed to be updated. The Task Force discussed ways to improve the site to provide more information to scientists wishing to obtain human embryonic stem cell lines for research. At the request of the Task Force, the NIH redesigned and updated the registry and continues to monitor and update the site as new information on the cell lines became available from the providers. In addition, the Task Force is examining and discussing considerations for having NIH establish a Stem Cell Repository.

Item

Physical inactivity - Physical inactivity, as a contributing factor to disease, represents the third leading cause of death in the United States and is a major contributor to obesity, the second leading cause of death. The Committee encourages the NIH to conduct public outreach efforts with the goal of encouraging researchers to bring their research expertise and skills to bear on this field. (Page 154)

Action taken or to be taken

The NIH has a very active research portfolio in the area of physical activity, and has recently launched a range of initiatives to bolster research in this area, encouraging investigators to apply their expertise to large clinical trials and innovative pilot studies that focus either directly on physical activity or include physical activity as a major component; the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute (NHLBI) are the major supporters of these efforts. A number of studies include physical activity in interventions to achieve and sustain weight loss as well as prevent obesity, to reduce risk for diabetes, and to control blood pressure. Studies are also testing effects of various amounts of physical activity on cardiovascular risk factors and cardiorespiratory fitness, and testing interventions to increase physical activity in diverse population groups. Further, the NIH promotes the importance of physical activity through a variety of public outreach efforts.

Highlights of NIH's research portfolio in this area:

In the Look AHEAD (Action for Health in Diabetes) multicenter clinical trial, researchers will investigate whether lifestyle interventions of exercise and decreased caloric intake--designed to produce voluntary, sustained weight loss in obese people with type 2 diabetes--will improve health, particularly with respect to cardiovascular outcomes. Look AHEAD is sponsored by the NIH and the Centers for Disease Control and Prevention (CDC).

The PREMIER study is testing an intervention for multiple lifestyle behaviors to control blood pressure, including weight loss and weight control, reduced dietary sodium, increased physical activity, and eating the DASH (Dietary Approaches to Stop Hypertension) dietary pattern. The study includes participants with high-normal blood pressure or stage 1 hypertension.

Researchers in the new Network for Type 2 Diabetes in Children and Adolescents are designing a school-based prevention trial to reduce risk factors for type 2 diabetes in children. This trial will include measures to increase physical activity, decrease sedentary activity, and improve diet. This clinical trials network is also developing a treatment trial that will include a physical activity component to complement pharmacological interventions.

The ACTION (A Congestive heart failure Trial Investigating Outcomes of Exercise) study will test the effects on morbidity and mortality of exercise training in patients with clinical heart failure.

Through a new NIH obesity-prevention program, researchers will collaborate with one or more community groups, such as schools, worksites, or other organizations, to develop and/or implement environmental modifications aimed toward increasing physical activity, decreasing sedentary behaviors, and improving diets.

A new Weight Loss Maintenance Trial will compare two strategies for maintaining weight loss in adults who have successfully lost weight. Both include a strong focus on increasing physical activity.

An NIH initiative is encouraging pilot clinical studies on obesity prevention, encompassing exercise and other interventions. Plans are being developed to implement larger trials of promising interventions that arise from these studies, which are nearing completion.

GEMS (Girls Health Enrichment Multi-site Studies) is testing interventions for decreasing excessive weight gain in African-American girls aged 8-10 years. Approaches to promotion of both increased physical activity and healthy eating patterns are being evaluated.

TAAG (Trial of Activity in Adolescent Girls) will test the effectiveness of a coordinated school and community-based intervention in preventing the decline in physical activity that typically occurs among girls during middle school.

Additional venues of NIH support for research in the area of physical activity: An NIH initiative is encouraging research on physical activity and obesity across chronic diseases. The NIH also supports investigator-initiated studies relating to physical activity, and recently sponsored a workshop on the interaction of physical activity and nutrition. The Small Business Innovation Research (SBIR) portfolio includes support for projects in this area. Finally, the NIH provides training and career development awards for research in this field.

Highlights of NIH-supported public outreach to promote physical activity:

The new “Small Steps, Big Rewards” campaign emphasizes that modest lifestyle changes, including physical activity and healthier diets, can help prevent the onset of type 2 diabetes. This campaign, which is part of the National Diabetes Education Program (sponsored by NIH and CDC), grew out of the findings of the NIH-sponsored Diabetes Prevention Program clinical trial.

An Obesity Education Initiative has been working to enhance research translation and education activities that address the increasing prevalence of overweight and obesity in

the population. Public outreach has included booklets, IQ quizzes, fact sheets, and tip sheets.

The NIH's Weight-control Information Network (WIN) has begun publishing a new series of booklets, in English and Spanish, on "Healthy Eating and Physical Activity Across Your Lifespan." Other WIN publications include "Active at Any Size" and "Walking: A Step in the Right Direction." WIN's "Sisters Together: Move More, Eat Better" theme encourages African American women to maintain a healthy weight through physical activity and healthy eating.

The nationwide community-based Hearts N' Parks program encourages increased physical activity and healthy eating.

Information on the importance of physical activity is incorporated into all of the materials for the public and health care providers issued by the National Cholesterol Education Program and the National High Blood Pressure Education Program. The National Asthma Education and Prevention Program also addresses the importance of physical activity in children suffering from asthma.

Item

Postpartum depression – Each year, over 400,000 women suffer from postpartum mood changes, with "baby blues" afflicting up to 80 percent of new mothers; postpartum mood and anxiety disorders impairing around 10-20 percent of new mothers; and postpartum psychosis striking 1 in 1,000 new mothers. However, little systematic research has been done to uncover the underlying causes and to develop effective treatments. Therefore, the Committee encourages the Institutes to expand, intensify and coordinate research on postpartum depression and psychosis. In addition, the Committee encourages the NIH to convene a national research conference to develop a national research plan for postpartum depression and psychosis. (p. 154/155).

Action taken or to be taken

In July 2002, the NIMH and the ORWH co-sponsored an international meeting on postpartum depression. The meeting brought together experts in the diagnosis, identification, and treatment of postpartum depression. The major goal of the meeting was to provide assistance to NIH staff in the development of an up-to-date clinical research agenda. In addition, another panel of experts at the meeting highlighted the importance of translational research linking neuroscience findings to clinical applications. Furthermore, in December 2002, an inter-agency group focusing on national efforts in the area of maternal health and comprised of representatives from major DHHS research and services agencies, identified postpartum depression as the first priority for their initial collaborations. Representatives from the National Institutes of Health (NIH), the Health Resources and Services Administration (HRSA), the Agency for Healthcare Research and

Quality (AHRQ), the Substance Abuse & Mental Health Services Administration (SAMHSA), the Food and Drug Administration (FDA) and the Center for Disease Control and Prevention (CDC) will work collaboratively in this area. CDC and NIMH will take the lead in preparing a scientific summary of the area and of agency activities; and in providing a public health rationale for the significance of the collaborative approach in DHHS. Additionally, the group will develop plans for future collaborations in the area of postpartum depression. These documents will be available in mid 2003.

Item

Racial and ethnic disparities – The Committee was disturbed by the conclusions of the Institute of Medicine’s March 2002 report titled “Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care.” The Committee strongly urges the NIH to take all steps necessary to reduce and eventually eliminate racial and ethnic health disparities. On a related matter, the Committee is pleased with the leadership that NIH has shown, through its Projecto Ciencia initiative, to provide state-of-the-art health material to Hispanic consumers and information to Hispanic health professionals on NIH research opportunities. The NIH is encouraged to increase funding for this initiative with expanded emphasis on outreach to Hispanic consumers, Hispanic participation in clinical trials, and NIH training and research opportunities, especially as principal investigators. (p. 155)

Action taken or to be taken

This past year the NIH Director and the NCMHD developed a strategic plan for coordinating NIH efforts to eradicate health disparities. The plan describes the scope of the problem of health disparities among the various minority and health disparities populations, specific objectives for addressing the problem and the methods for advancing those objectives and for evaluating progress. Representing the collective commitment of the NIH ICs, the plan includes submissions from all NIH ICs that highlight their areas of emphasis, objectives, action plans, timelines and performance measures in three major areas: 1) research, 2) research infrastructure, and 3) outreach. **The Strategic Research Plan, an evolving document, will be revised annually based on public comments received, public health need, scientific opportunity, and other factors. The Strategic Plan is undergoing final revision based on comments by the Department of Health and Human Services and will be forwarded to Congress in early 2003.**

The NCMHD is pleased to support the Projecto Ciencia Initiative, which enabled the National Alliance for Hispanic Health to 1) establish a communication infrastructure for reaching Hispanic scientists; 2) establish a forum for communication between scientists and Hispanic community-based leadership; and 3) expand the pipeline of Hispanic scientists applying for NIH research grants and professional development opportunities. The NCMHD has expanded its commitment to serving the Hispanics community by initiating a number of projects: 1) The Partnership for Excellence in Cancer Research is a long-term partnership between the University of Texas, the M D. Anderson Cancer Center and the University of Puerto Rico Cancer Center to support cancer research,

training, and career development designed to benefit the Hispanic community and other minority population. 2) The National Latino and Asian American Study whose goal is to estimate the lifetime and 12-month prevalence of psychiatric disorders and the rates of mental health services used for the Hispanic population in the U.S. will generate useful data for planning mental health services. 3) The HACU National Internship Program provides challenging professional and educational experiences in the federal sector to qualified students from Hispanic Serving Institutions. 4) The National Hispanic Youth Initiative is a rigorous program designed to support Hispanic students enrolled in academic programs in the allied health professions through lectures, round table group discussions on health care issues and scientific research, academic preparation, and training opportunities in health care, research, health legislation, and public policy. It is hoped these efforts will ensure an increase in the number of Hispanic health care professionals serving the Hispanic community. The NCMHD is also supporting research projects focused on health disparities in the Hispanic community. One example, Bacteria-Host Cell Interactions in Periodontal Disease, is investigating why periodontal disease prevalence is high in Hispanics and African Americans.

Item

Scleroderma – The Committee has included specific report language on scleroderma under NIAMS and the NHLBI, but it recognizes that scleroderma research involves many other Institutes and Centers as well. The NIDDK is encouraged to support such research because of scleroderma's links to gastrointestinal involvement and renal crisis; the NIDCR, because scleroderma may be associated with a number of potential dental and craniofacial complications; and the Office of Research on Women's Health, because scleroderma mainly strikes young women. (p. 155)

Action taken or to be taken

Scleroderma results from the abnormal growth of connective tissue, which supports the skin and internal organs. In some forms of scleroderma, hard, tight skin is the extent of the disease. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs, such as heart, lungs, and kidneys. In scleroderma, the immune system is thought to stimulate cells called fibroblasts to produce excess collagen. Currently, there is no treatment that controls or stops the underlying problem: the overproduction of collagen. Little is known about the cellular changes that cause the skin and organs to harden, and the disease may be difficult to diagnose. Because the disease can affect multiple organ systems, several NIH components, including NIAMS, NHLBI, NIDDK and NIDCR, have an interest in scleroderma research and in high-quality applications for studies that are relevant to their respective missions.

Understanding the early cellular and molecular changes that precede scleroderma is critical to developing effective treatments. In response to this need, in the fall of 2001, the NIAMS awarded ten new grants to support research into the causes of scleroderma and to bring us closer to finding treatments. Two of these awards were co-funded by the NIH Office of Research on Women's Health. For example, one study is investigating the molecular basis for the closing down of blood vessels, which is a leading cause of death in scleroderma. Other researchers are examining

mouse models to uncover the processes that cause collagen to accumulate, and whether persistent bacterial infection of the skin or small blood vessels is a potential cause of scleroderma. The underlying mechanisms of the cell transfer that occurs between mother and child in scleroderma is also under investigation. New projects in this area include studies of blood cells from scleroderma patients and nonaffected individuals to determine their origin and role in the development of this disease, as well as investigations of immune cells known as T cells in the skin of women and children with scleroderma. With respect to innovative therapies, the effectiveness of ultraviolet phototherapy for the treatment of localized forms of scleroderma is being tested, and work is underway in mouse models to study the early inflammatory events of skin fibrosis. Other studies are looking at the effect of race and ethnicity on scleroderma. In addition, the NIAMS currently supports two specialized centers of research in scleroderma, as well as a multidisciplinary clinical research center focused on pediatric rheumatic diseases, such as juvenile scleroderma. Finally, behavioral scientists supported by the Institute have found that managing pain and depression may lead to improved functioning and quality of life for patients with scleroderma.

Approximately 80 percent of scleroderma patients will eventually develop some degree of lung involvement, with restrictive lung disease (interstitial pulmonary fibrosis) now being the leading cause of morbidity and mortality in scleroderma patients. In collaboration with the NIAMS, the National Heart, Lung, and Blood Institute (NHLBI) is currently supporting a multicenter, randomized clinical trial to determine the effectiveness of cyclophosphamide in slowing the progression of lung disease in patients with scleroderma. The NHLBI also supports a major program of basic and clinical research on the etiology and pathogenesis of interstitial pulmonary fibrosis, which is expected to be beneficial in understanding lung fibrosis associated with scleroderma. Furthermore, NIDDK contributes to the science of scleroderma by supporting a large program devoted to research aimed at understanding the basic mechanisms that control motility of the gastrointestinal tract, which is impaired in patients with this disease.

Item

Sjögren's Syndrome – Sjögren's syndrome is one of the most prevalent autoimmune diseases, yet little is known about the cause or effective treatments. The Committee is pleased by the research that the NIDCR has conducted on Sjögren's, but recognizes that because this disease may affect all organs, it falls within the mission of many Institutes. For this reason, the Committee urges the NIH Autoimmune Diseases Coordinating Committee, as it implements the NIH Autoimmune Diseases Research Plan, to emphasize increased research on Sjögren's syndrome across the Institutes. In particular, the Committee encourages the NIAMS and NIAID to expand their research on musculoskeletal and immunological manifestations of the disease. The Committee also notes that Sjögren's syndrome is an excellent model for lymphoproliferation and transformation to malignancies; therefore, the NCI is encouraged to explore the increased progression in Sjögren's from a benign autoimmune process to malignancy. (p. 155)

Action to be taken

NIH Autoimmune Diseases Research Plan

The National Institutes of Health (NIH) Autoimmune Diseases Research Plan, which was transmitted in December 2002, highlights many unprecedented opportunities to increase the understanding of autoimmune diseases, including Sjögren's syndrome, with a conceptual focus on the underlying mechanisms shared by many autoimmune diseases.

Understanding how these diseases are alike may facilitate the translation of new knowledge into more effective treatment and prevention strategies. The Plan describes four areas central to progress for all autoimmune diseases research: burden of disease; etiology; treatment, prevention, and diagnosis; and training, education, and information dissemination; and offers recommendations for addressing each area.

The NIH Autoimmune Diseases Research Plan was prepared by the NIH Autoimmune Diseases Coordinating Committee (ADCC) and reviewed by an expert panel that included scientists, clinicians, and representatives from constituency groups. The ADCC, which was established in 1998, under the direction of the National Institutes of Allergy and Infectious Diseases (NIAID), facilitates collaboration among the NIH Institutes, Offices, and Centers, other Federal agencies, and private organizations with an interest in autoimmune diseases. In FY 2003, the NIH ADCC will continue its efforts to coordinate and enhance autoimmune diseases research between the various Federal and private entities that conduct autoimmunity research, education, and outreach, including implementation of the recommendations of the NIH Autoimmune Diseases Research Plan.

NIDCR-Funded Research

NIDCR continues to conduct research to increase our understanding of Sjögren's syndrome. Sjögren's syndrome is an autoimmune disorder whereby the immune system attacks and often seriously damages the patient's own salivary glands and tear glands, leading to oral and ocular dryness.

The Institute has initiated efforts to construct a registry of Sjögren's syndrome patients. Such a registry should help establish an adequately sized, well-defined study population that can serve to establish clinical outcomes for new treatments or determine the genetic basis for the disease. Such patient registries have proven to be enormously valuable for studies of conditions like systemic lupus erythematosus and should greatly facilitate progress in our understanding and treatment of Sjögren's syndrome.

Studies on the natural history of the disorder are adding to our knowledge of the disease by following the status of individual patients over time, and has allowed for the development of non-biopsy measures to monitor disease progress. Other studies are working to define how salivary gland proteins become autoimmune targets, which is an essential step in the process to develop specific new treatments. Meanwhile, other Institute scientists are conducting pilot clinical trials of the hormone DHEA, and the compound etanercept to determine if these are safe and potentially effective treatments.

NIDCR-supported scientists are working on the development of an artificial salivary gland for individuals whose salivary glands have been completely destroyed by either Sjögren's syndrome, or by radiation treatment for head and neck cancers. The goal is to

implant cells, which have been engineered to secrete a saliva-like fluid, on a biodegradable matrix in the patients' cheeks. Scientists believe that the artificial salivary gland will be ready for clinical testing within 5-7 years. These same scientists are also developing a gene therapy approach for treating patients whose salivary glands are only partially damaged. This involves delivering the genes non-invasively into glands through a tiny opening inside the cheek (where the saliva normally exits). They have had considerable success in animal models and are methodically working toward clinical trials.

NIAID-Funded Research

NIAID is committed to furthering the understanding of the immunopathogenesis of autoimmune diseases, including Sjögren's syndrome, and to promoting the application of basic research to clinical investigations. In addition to NIAID's investment in investigator-initiated research on autoimmune diseases, the Institute has established large, multidisciplinary research programs that focus on the immunological aspects of these diseases, including Sjögren's syndrome. Among these programs are the Autoimmunity Centers of Excellence, Centers for Prevention of Autoimmune Diseases, Immune Tolerance Network, and the Multiple Autoimmune Diseases Genetics Consortium. Research supported by these programs includes efforts to understand the genetics of autoimmunity; elucidate the mechanisms by which the immune system recognizes and tolerates one's own cells (self-tolerance); develop approaches to induce self-tolerance, and characterize the pathways through which the immune system mediates the destruction of tissue.

NCI-Funded Research

The National Cancer Institute (NCI) is interested in Sjögren's syndrome as a means of elucidating genetic and molecular mechanisms of cancer. The NCI is specifically interested in autoimmune diseases and their relationship to cancer. Among all autoimmune diseases, Sjögren's syndrome best illustrates the autoimmunity-lymphoproliferation-lymphoma sequence. A representative of the NCI has been an active participant in the NIH Autoimmunity Diseases Coordinating Committee and is exploring the role of immune tumor regression as a form of autoimmune response to cancer.

NIAMS-Funded Research

The NIAMS has a major interest and investment in autoimmune diseases, such as Sjögren's syndrome. The Institute is an active member of the Autoimmune Diseases Coordinating Committee, and supports a broad range of research on autoimmune conditions, from basic science investigations to genetics studies to prevention research. For example, the NIAMS currently funds work to better understand the molecular basis of autoimmune diseases such as Sjögren's and systemic lupus erythematosus, another condition in which the body's immune system goes awry; studies to identify genes that predispose individuals to autoimmunity; and efforts to develop animal models which will provide new insights into the human form of diseases such as Sjögren's. These activities will enhance our knowledge of the underlying causes of autoimmunity, and point the way

to new treatment approaches for Sjögren's syndrome and related conditions.

Item

Stem cell research - The Committee also commends NIH for the development of the online human embryonic stem cell registry and encourages NIH to expand the registry to make it more useful to researchers by providing additional documentation regarding the stem cell lines, such as conditions of derivation, characteristics of the cell lines (i.e., cell surface markers present or absent, growth conditions, and requirements for maintenance in long-term culture), and publications that reference the cell lines. Furthermore, the Committee encourages NIH to seriously consider developing a stem cell repository.

In addition, the Committee is aware of the exciting new developments in the field of umbilical cord stem cells. But more research needs to be undertaken to explore these issues, including the possible use of these cells to treat cancers, genetic diseases, muscular dystrophy, neurological disorders, and diabetes. The Committee urges the NCI, NHLBI, NIAMS, NIDDK and the NINDS to actively pursue research in these areas in a manner consistent with the NIH tradition of strong peer reviewed science. (p. 155/156)

Action taken or to be taken

The NIH has made considerable progress in moving the stem cell research agenda forward during the last year. In August 2002, Dr. Elias Zerhouni, NIH Director, appointed Dr. James Battey, Director of the NIH/National Institute on Deafness and Other Communication Disorders, as chair of the NIH Stem Cell Task Force. The mission of the Task Force is to enable and accelerate the pace of stem cell research by identifying rate limiting resources (both material and human), and develop initiatives to enhance these resources. The NIH Stem Cell Task Force seeks the advice of scientific leaders in stem cell research about the challenges in moving the stem cell research agenda forward, and strategies NIH may pursue to overcome these challenges. The Task Force is made up of leading scientists at NIH who appreciate the opportunity of stem cells to inform NIH in the near future about the fundamental processes of differentiation and development, which may ultimately lead to new therapeutic strategies.

At a recent meeting of the Task Force, the group agreed that the online NIH Human Embryonic Stem Cell Registry needed to be updated. The Task Force discussed ways to improve the site to provide more information to scientists wishing to obtain human embryonic stem cell lines for research. At the request of the Task Force, the NIH redesigned and updated the registry and continues to monitor and update the site as new information on the cell lines becomes available from the providers. In addition, the Task Force is examining and discussing considerations for having NIH establish a Stem Cell Repository.

The NIH is actively supporting research in many areas of stem cell biology to uncover the promise of potential therapies for cancers, genetic disease, muscular dystrophy, neurological disorders, and diabetes. For example, NIAMS-supported scientists have isolated special muscle-generating stem cells that can improve muscle regeneration and deliver a missing protein to damaged muscles in animal models of Duchenne muscular

dystrophy (DMD). The research involves the isolation of a sub-population of muscle stem cells with special characteristics. When these cells were transplanted into the animal, numerous dystrophin muscle fibers developed, suggesting that the transplanted cells could help restore function for a time. The results may also indicate that some of the major obstacles to muscle cell transplantation -- low cell survival rate, poor spreading of cells, and cell rejection by the immune system -- are being overcome. This could develop into treatment for all forms of muscular dystrophy (MD) and other muscle-related diseases.

Several NIH Institutes are studying the basic biology and genetic structure of umbilical cord blood stem cells with the hope of developing transplantation procedures with lower incidence of infections or rejection. NHLBI is actively studying cord blood as an alternative to adult marrow for transplantation. Through the NHLBI's Cord Blood Transplantation Study (COBLT), contractors have banked more than 8,000 frozen umbilical cord units which have resulted in transplants to more than 200 patients, most of them children with leukemia. Using cord blood makes it easier to find a donor for a given patient, because the blood does not need to be matched as closely as does bone marrow. This has increased availability of transplants for members of racial/ethnic minority groups, for whom finding a match has traditionally proven difficult. In the COBLT study, 95 percent of patients have been able to find a suitable donor. Preliminary COBLT results have shown that cord blood cells can engraft in patients with refractory leukemia and cure the disease in some patients. However, the limited number of cord blood cells in a unit often leads to failure of sufficient cell growth in the patient and limits the clinical utility to the pediatric population. In studying mouse models, transplanting cells from more than one donor hastens growth of donor cells when the cell dose is small. Research studies are underway to identify cell culture conditions that may allow expansion of the number of umbilical cord stem cells in vitro, making this technology useful for a broader spectrum of disease and patients.

NIDDK is currently recruiting patients for a study to procure umbilical cord blood from newborns at risk for sickle cell disease. In addition, cord blood samples from newborns with sickle cell trait are being studied in order to develop methods for processing and cryopreserving umbilical cord blood stem cells for use in potential gene therapy trials. The control samples will also be used to establish optimal gene transfer methods to ensure stable, high level, long-term gene expression.

Item

***Stroke in women* --As the second-leading cause of death among women worldwide, stroke in women is a major health problem. The Committee believes that special attention should be focused on better understanding the gender differences in stroke and cerebrovascular disease, as well as in the medical care of stroke patients. Some aspects of the disease unique to women include strokes related to pregnancy and the use of oral contraceptives; stroke in younger women therefore should not be underestimated. Stroke is additionally a leading cause of serious disability among women and may contribute to late-life cognitive decline. The Committee supports the funding of new and continuing NIH studies that investigate the impact of postmenopausal hormone replacement therapy on stroke risk. The Committee urges**

the NIH to increase research in stroke among women of all ages, with a focus on stroke prevention, acute stroke management, post-stroke recovery, long-term outcomes, and quality of life.

In addition, the Committee supports the NIH's initiatives toward advancing the organization of stroke care and the identification of stroke treatment and research centers that would provide rapid, early, continuous 24-hour treatment to stroke victims, including the use of the clot-buster t-

PA when appropriate. The Committee believes that designated areas in medical facilities equipped with the resources and personnel for treating stroke would also promote the early evaluation of innovative stroke treatments. (p. 156)

Action taken or to be taken

It has been noted that the incidence of cardiovascular disease in women increases dramatically following menopause, most likely triggered by estrogen deprivation. By studying animals, investigators are trying to establish a link between estrogen and brain control of blood pressure, which when elevated, is a risk factor for stroke. Also, animal studies have shown that females experience significantly decreased brain injury after experimental stroke compared to males; however, removal of the ovaries—the principal source of estrogen—eliminates the protection. Investigators are looking specifically at gender differences and the role estrogen in protection from neuronal injury following stroke.

Over the last several years, anecdotal evidence had suggested that hormone therapy in menopausal women may confer some protection against heart disease and stroke.

In 2001, an NINDS-sponsored trial showed that estrogen replacement therapy does not reduce the risk of stroke or death in postmenopausal women who have already had a stroke or a transient ischemic attack. In July 2002, the investigators involved in the large NIH-funded controlled clinical study, the Women's Health Initiative, reported that they had found small increases in breast cancer, coronary heart disease (CHD), stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. For these reasons, the study was halted. It is expected that additional research will be conducted to explain the differences seen in animals that were not replicated in human studies, and further clarify role of estrogen on stroke in women.

NINDS supported investigators are conducting clinical studies attempting to determine if there is an elevated risk of a first stroke in patients with systemic lupus erythematosus ("Lupus"), an autoimmune disease that strikes predominately women. Recently, these investigators published a scientific article examining how certain antibodies may be a risk factor for stroke in young women.

Regarding stroke care, the NINDS has launched the *Specialized Program of Translational Research in Acute Stroke (SPOTRIAS.)* The objective is to facilitate translation of basic research findings into clinical practice in settings where patients with acute ischemic and hemorrhagic stroke are evaluated and treated very rapidly

after the onset of their symptoms. The intent of the SPOTRIAS is to support a collaboration of clinical researchers from different specialties whose collective efforts will lead to new approaches to early diagnosis and treatment of acute stroke patients.

Item

Training award stipends – The Committee concurs with the policy adopted by the NIH in March 2001 which provides for 10 percent increases in research training award stipends until appropriate stipend levels are achieved. The Committee strongly encourages the NIH to apply this policy to the fiscal year 2003 appropriation, just as it did with the training stipends funded by the fiscal year 2002 appropriation. (p. 157)

Action taken or to be taken

The NIH appreciates the Committee's support for the plan to raise the stipends provided under the Ruth L. Kirschstein National Research Service Award program. Over the past five years (1998 - 2002), predoctoral stipends have increased close to 55 percent, from \$11,748 to \$18,150. Similarly, postdoctoral stipends have increased by almost 50 percent during this same period. On a graduated scale based on experience, a postdoctoral stipend increased from \$21,000 to \$31,092 for a trainee with 0 years of experience, and

from \$33,012 to \$48,852 for a trainee with seven or more years of experience. The FY 2003 Amended President's budget request will provide an increase of 4 percent for predoctoral and postdoctoral stipends for NRSA trainees.